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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,580	03/29/2007	Shyam S. Mohapatra	USF.208TCXC1	6999

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
02/01/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,580	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 12/23/10.

Claims 12-14, 44, and 45 remain pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-14, 44, and 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over McSwiggen et al (US Patent 5,693,532) in view of Tuschl et al (US 20040259247 A1), and Chen et al (US 20040242518).

McSwiggen taught methods of inhibiting the replication of RSV in vivo in infected humans through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. In one embodiment, the ribozymes are targeted to NS1 transcripts. See columns 2-3, for example (e.g. paragraph bridging columns 2 and 3). Preferred administration is by aerosol inhalation which would provide delivery to the airways (see column 9, lines 8-16). The ribozymes can be expressed from vectors (column 5, lines 10-12 and 27-52) under the control of eukaryotic pol I, pol II, or pol III promoters (column 9, lines 17-27).

McSwiggen did not teach administration of siRNA encoding vectors, or administration to a subject not suffering from RSV infection (instant claim 14).

Tuschl taught methods and materials for making and using short, double stranded interfering RNAs (siRNAs) against virtually any known gene for both research and clinical use. It is said the target gene to which the RNA molecule of the invention is directed may be a viral gene associated with a pathological condition (paragraph 30). The siRNAs consist of sense and antisense strands of between 19 and 25 nucleotides in length, wherein the antisense strand is complementary to a target gene (cols. 1-3). Tuschl taught and/or suggested both in vitro transfection and in vivo delivery of siRNAs for therapeutic purposes (pages 3-4, and see examples). Thus, Tuschl provided a general blueprint for the design, synthesis, and application of short interfering RNAs.

Tuschl also directly compared and contrast ribozyme and RNAi technologies, stating at paragraph 148 that "…siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments."

Chen taught the use of siRNA expression vectors to inhibit viral infection in human lungs. Chen exemplified the use of siRNA expression vectors to prophylactically inhibit influenza infection in mouse lung. DNA expression vectors encoding siRNA directed to influenza virus transcripts were administered to mice, followed by administration of PR8 influenza virus. Fig. 26 shows that lower virus titers were observed when mice were given plasmid DNA that expressed either NP-1496a shRNA

or PB1-2257 shRNA. The virus titers were more significantly decreased when mice were given both influenza-specific plasmid DNAs together, one expressing NP-1496a shRNA and the other expressing PB1-2257 shRNA. These results show that shRNA expressed from DNA vectors can be processed into siRNA to inhibit influenza virus production in vivo. See paragraphs 58, 185, 214, and Example 14 at paragraphs 429-437. Chen also taught that viral vectors could be used to delivery siRNAs (paragraphs 9, 55, 91, 161-164, 252. Chen envisioned delivery to humans (paragraphs 88, 156, and 248).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNAs directed against RSV N1 for the N1-directed ribozymes of McSwiggen in order to inhibit the expression of an RSV mRNA, and to use the vectors of Chen to express them in the human lung in vivo. One of skill would have been motivated to do so because Tuschl taught that siRNAs are in general significantly more potent than ribozymes. In view of the fact that Chen demonstrated that siRNA expression vectors targeting influenza virus could be delivered to the mouse lung in vivo and reduce the titre of the target virus, one of skill would have reasonably expected that siRNAs targeted to RSV could be successfully delivered and expressed in vivo as well, and so would have had a reasonable expectation of successfully inhibiting RSV NS1 expression and RSV replication, leading to a reduction in viral titer and an alleviation of symptoms.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the siRNA expression vectors to a subject not suffering from

RSV infection in order to prevent infection, and would have had a reasonable expectation of success in view of the results of Chen who showed that expression of anti-influenza siRNAs prior to infection decreased the titer of subsequently infecting influenza virus. It is noted that a RSV NS1 expression is considered to be a symptom of RSV infection, thus one of ordinary skill would have expected to achieve alleviation of that symptom in practicing the method of McSwiggen as modified by Tuschl and Chen.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 12/23/10 have been fully considered but they are not persuasive.

Applicant asserts that the cited references do not establish a correlation between the disclosed procedures and a reduction in RSV viral titer in the human airway. Applicant asserts that McSwiggen and the other cited references provide no empirical data in vitro or in vivo to establish a proof of concept with ribozymes or any nucleic acid inhibitor to inhibit RSV in the respiratory epithelial cells, and that absent such empirical data one of ordinary skill would have had no reasonable expectation of success. This argument is unpersuasive. As Applicant states at page 5 of the response, obviousness requires at least some degree of predictability, but does not require absolute predictability. In this case, Chen had shown that delivery of siRNA expression vectors to mouse lung in vivo provided expression of siRNAs in respiratory epithelial cells and inhibition of influenza virus infection. As discussed above, this would have provided a

reasonable expectation of successfully expressing siRNAs in respiratory epithelial tissue in a human. Those of ordinary skill in the art appreciated that siRNA technology generally provided more potent expression inhibition than did the ribozyme technology of McSwiggen (see Tuschl, above). Absent evidence that RSV provided any special problems in the context of siRNA inhibition, one of skill would have reasonably expected to be able to inhibit expression of targeted RSV genes in a human by following the teachings of Chen and using siRNAs targeting RSV instead of influenza. A proof of concept is not required to provide a reasonable expectation of success, all that is needed is a reasonable expectation of success.

As applicant notes at page 5, evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. However, no such evidence is provided in this case. On the other hand, the cited art shows that siRNAs can be expressed in vivo to inhibit viral influenza, and there was sufficient guidance and motivation in the prior art to develop a similar approach for RSV by targeting RSV NS1 expression.

Applicant also asserts that one of ordinary skill would have had no reasonable expectation of reducing RSV titer when relying on the cited prior art, and that the claimed invention provides unexpected results by augmenting anti-RSV host immunity via enhanced host IFN production which prevents mice from reinfection. This is unpersuasive because McSwiggen taught that NS1(referred to as 1C) was required for the viral life cycle (column 7, lines 9-15). One of ordinary skill would have reasoned that a decrease in a protein that was required for the viral life cycle would necessarily lead to

a reduction in viral titer. Moreover, the document to which Applicant claims priority (60/481,738) states at paragraph 12 that "RSV NS1 and NS2 genes are known to interfere with type-1 IFN response." This appears to be an evaluation of the state of the art at the time of the invention. If it was known that RSV NS1 interfered with the cellular interferon response to viral infection, then it would not be unexpected that inhibition of NS1 might improve the cellular immune response and result in a decrease in viral titer. Indeed, Bossert (2002, of record in the IDS of 9/18/09, citation R36) disclosed that NS1 proteins from human and bovine RSVs mediated RSV resistance to host interferons in a host-specific manner. More specifically, Bossert showed that a chimeric bovine RSV in which human NS1 and NS2 had been substituted for bovine NS1 and NS2 provided resistance to interferon-mediated anti-viral responses, but that both NS1 and NS2 proteins were required for this effect. See abstract; first sentence of paragraph bridging pages 4287 and 4288; page 4287; first full paragraph on page 4288; paragraph bridging pages 4288 and 4289; first full paragraph on page 4291; and page 4292, left column. Thus one of ordinary skill in the art at the time of the invention would have had reason to expect that inhibition of RSV NS1 expression would have relieved RSV inhibition of host interferon activity, leading to a reduction in titer.

While Applicant is correct in indicating that the perception of siRNA effectiveness in the prior art does mean that siRNAs will necessarily be effective in every setting, in this case there is sufficient teaching in the cited art, and knowledge in the art in general, to provide one of ordinary skill with a reasonable expectation that the one could have practiced the invention as claimed. It clearly would have been obvious to develop

siRNAs directed against NS1 in view of the teachings of McSwiggen and Tuschl. There was a reasonable expectation that such siRNAs would inhibit RSV NS1 expression, in the absence of evidence to the contrary, in view of the general state of the art of siRNA technology as expressed by Tuschl. Chen demonstrated that prior art technology was available for one to deliver siRNA expression vectors to respiratory epithelial cells in vivo and achieve expression and activity of encoded siRNAs. Thus, one of ordinary skill in the prior art would have had reason to believe that RSV NS1 expression could have been inhibited by delivery of RSV NS1 siRNA expression vectors to human airway cells in vivo. Finally, as evidenced in the priority document and the prior art of record, those of ordinary skill were aware of the relationship between NS1 and host interferons such that an increase in host immune response against RSV due to NS1 inhibition would not necessarily have been unexpected.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's acting supervisor, Heather Calamita, can be reached at (571) 272-2876. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Richard Schnizer/
Primary Examiner, Art Unit 1635